Targeting HbA1c in diabetes management: What are the key lessons from glucose lowering trials

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Aachen, Germany
Heart Failure: The next frontier for SGLT2 inhibitors?

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Conflict of interest
Nikolaus Marx

• **Speaker:** Amgen, Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, Lilly, NovoNordisk

• **Research grant:** Boehringer Ingelheim, MSD

• **Advisory board:** Amgen, Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, NovoNordisk

NM declines all personal compensation from pharma or device companies
Heart Failure: The next frontier for SGLT2 inhibitors?

- Heart failure in diabetes
- SGLT2 inhibition and heart failure
- Effects of SGLT2 inhibitors in subjects without diabetes
Systolic heart failure =

HFREF (Heart failure with reduced ejection fraction)

Systolic heart failure:
- reduced contractile function

Normal

Dilatative cardiomyopathy
Diastolic heart failure =
HFPEF (Heart failure with preserved ejection fraction)

Diastolic heart failure:
- reduced relaxation
- impaired ventricular filling

Normal

Hypertrophic cardiomyopathy
Heart failure in diabetes

HF incidence by age group

- Diabetes
- No diabetes

Nichols GA et al. Diabetes Care 2004;27:1879

HF mortality in diabetes

~ 55%

Gustafsson et al. JACC 2004; 43:771-777
Impact of diabetes on outcomes in patients with HFrEF and HFpEF (CHARM program)

CV death or HHF in patients with or without diabetes based on ejection fraction category

- Increased risk for mortality and hospitalisation for HF in HF patients with diabetes
- HFpEF prognosis better than HFrEF
Heart failure with recurrent hospitalisation and a high risk for CV death and total mortality is the leading problem in type 2 diabetes in 2019!
Free fatty acids $\uparrow$

Insulin resistance

Hyperinsulinemia

Hyperglykämie

Myocardial hypertrophy

Altered myocardial metabolism
Fatty acid oxidation $\uparrow$

Myocardial energy production $\downarrow$

Decreased Ca handling

Myocardial apoptosis
Fibrosis

Oxidative stress

AGE deposition

Hexosamine pathway $\uparrow$
Altered myocardial Ca levels

Inflammation $\uparrow$

Myocardial hypertrophy

Microangiopathy
Myocardial stiffness

Impaired systolic function

Diabetic cardiomyopathy

Impaired diastolic function

after Savvaidis, Marx, Schütt
Der Diabetologe 2015; 11:379-387
Heart Failure:
The next frontier for SGLT2 inhibitors?

- Heart failure in diabetes
- SGLT2 inhibition and heart failure
  - Data from CVOTs
  - Patients with or without HF at baseline
  - Time course of risk reduction
  - Patients with or without HFrEF
- Effects of SGLT2 inhibitors in subjects without diabetes
SGLT2-Inhibition

Increased glucose filtration

Glomeruli

Increased glucose reabsorption

Proximal tubule

SGLT2 inhibitor

Increased urinary sodium excretion (temp.)

Increased urinary glucose excretion

After Marx et al. Eur Heart J 2016; 37(42):3192-3200
## CVOTs with SGLT2 inhibitors

### Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline Variables</th>
<th>EMPA REG (Empagliflozin)</th>
<th>Integrated CANVAS Program (Canagliflozin)</th>
<th>DECLARE (Dapagliflozin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (n)</td>
<td>7,034</td>
<td>10,142</td>
<td>17,160</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>Diabetes Duration (y)</td>
<td>57% &gt; 10 y</td>
<td>13.5 y</td>
<td>10 y</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31</td>
<td>32.0</td>
<td>32</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>8.1</td>
<td>8.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Prior CVD (%)</td>
<td>99</td>
<td>64.8</td>
<td>40</td>
</tr>
<tr>
<td>Prior HF</td>
<td>10</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>
Empagliflozin, canagliflozin and dapagliflozin reduce the combined endpoint of heart failure hospitalisation and CV death.
Reduction of heart failure hospitalisation by SGLT2 inhibitors

**EMPA-REG Outcome**

HR 0.65
(95%CI 0.50-0.85)
p=0.0017

**Canvas Program**

HR 0.67
(95%CI 0.52-0.87)

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Reduction of heart failure hospitalisation by SGLT2 inhibitors

DECLARE

Empagliflozin, canagliflozin and dapagliflozin reduce heart failure hospitalisation
### EMPA-REG OUTCOME

#### 3P-MACE and single endpoints

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with event/analysed</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>0.86</td>
<td>(0.74, 0.99)*</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>0.62</td>
<td>(0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>0.87</td>
<td>(0.70, 1.09)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>1.24</td>
<td>(0.92, 1.67)</td>
<td>0.1638</td>
</tr>
</tbody>
</table>

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction *95.02% CI
# CANVAS Program

## 3P-MACE and single endpoints

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with event/analysed</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3P-MACE</td>
<td>Canagliflozin: 585/5795, Placebo: 426/4347</td>
<td>0.86 (0.75, 0.97)</td>
<td>&lt;0.001 (non-inferiority) 0.02 (superiority)</td>
</tr>
<tr>
<td>CV death</td>
<td>Canagliflozin: 268/5795, Placebo: 185/4347</td>
<td>0.87 (0.72, 1.06)</td>
<td>NR*</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>Canagliflozin: 215/5795, Placebo: 159/4347</td>
<td>0.85 (0.69, 1.05)</td>
<td>NR*</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>Canagliflozin: 158/5795, Placebo: 116/4347</td>
<td>0.90 (0.71, 1.15)</td>
<td>NR*</td>
</tr>
</tbody>
</table>

Favours canagliflozin  | Favours placebo

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*NR* indicates not reported.
Empagliflozin but not canagliflozin or dapagliflozin reduce CV death in the respective outcome trials.
Heart Failure: The next frontier for SGLT2 inhibitors?

- Heart failure in diabetes
- SGLT2 inhibition and heart failure
  - Data from CVOTs
  - Patients with or without HF at baseline
  - Time course of risk reduction
  - Patients with or without HFrEF
- Effects of SGLT2 inhibitors in subjects without diabetes
Empagliflozin, canagliflozin, and dapagliflozin reduce heart failure hospitalisation and CV death in patients with or without heart failure at baseline.
Heart Failure: The next frontier for SGLT2 inhibitors?

• Heart failure in diabetes

• SGLT2 inhibition and heart failure
  – Data from CVOTs
  – Patients with or without HF at baseline
  – Time course of risk reduction
  – Patients with or without HFrEF

• Effects of SGLT2 inhibitors in subjects without diabetes
Reduction in CV mortality was immediate, with benefit sustained throughout the trial.

**EMPA-REG Outcome**

**Hazard ratio over time**

<table>
<thead>
<tr>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.62</td>
<td>(0.49, 0.77)</td>
<td>&lt;0.0001</td>
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</table>

Placebo | Empagliflozin

- **HR 0.62** (95% CI 0.49, 0.77); p<0.0001
- Hazard ratio over time favours empagliflozin.
Reduced risk of HHF was observed early and sustained throughout the trial

**EMPA-REG Outcome**

**Hazard ratio over time**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio</td>
<td>0.65</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>0.50, 0.85</td>
</tr>
<tr>
<td>p</td>
<td>0.0017*</td>
</tr>
</tbody>
</table>

No. of patients:
- Empagliflozin: 4687, 4614, 4523, 4427, 3988, 2950, 2487, 1634, 395
- Placebo: 2333, 2271, 2226, 2173, 1932, 1424, 1292, 775, 168

Censoring relative to randomisation (days):
- Placebo better
- Empagliflozin better
Heart Failure: The next frontier for SGLT2 inhibitors?

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  – Data from CVOTs
  – Patients with or without HF at baseline
  – Time course of risk reduction
  – Patients with or without HFrEF

• Effects of SGLT2 inhibitors in subjects without diabetes
Prespecified analysis planned to examine the clinical benefit of dapagliflozin in patients with and without HFrEF

DECLARE-TIMI-58
N=17,160

HFrEF
EF <45%, N=671

Not HFrEF
N=16,489

History of HF

No History of HF

HF without known rEF
- EF≥45%, N=808
- EF unknown, N=508
N=1,316

No HF
N=15,173

1EF available in 5202 pts

Kato et al; Circulation 2019 online
Combination of CV death / HHF (by HFrEF vs not HFrEF subgroups)

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (95% CI)</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFrEF</td>
<td>0.62 (0.45; 0.86)</td>
<td>0.046</td>
</tr>
<tr>
<td>Not HFrEF</td>
<td>0.88 (0.76; 1.02)</td>
<td></td>
</tr>
</tbody>
</table>

Not HFrEF defined as pts with HF without known reduced EF and pts without hx of HF
- Treatment with dapagliflozin resulted in a lower rate of HHF vs placebo in a broad spectrum of patients including those with preserved EF.
- Dapagliflozin reduced CV death in patients with HFrEF, but not in those without HFrEF.
Heart Failure:
The next frontier for SGLT2 inhibitors?

• Heart failure in diabetes

• SGLT2 inhibition and heart failure

• Effects of SGLT2 inhibitors in subjects without diabetes
Patients with heart failure have similar pathophysiological features as patients with diabetes

<table>
<thead>
<tr>
<th>Heart failure</th>
<th>Shared pathological features</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired contractility</td>
<td>Endothelial dysfunction</td>
<td>Hyperglycaemia</td>
</tr>
<tr>
<td>Cardiomyocyte apoptosis/fibrosis</td>
<td>Insulin resistance</td>
<td>↓ Pancreatic beta-cell function</td>
</tr>
<tr>
<td>Neurohormonal activation</td>
<td>Mitochondrial dysfunction</td>
<td>Advanced glycated end-product toxicity</td>
</tr>
<tr>
<td>LV remodelling</td>
<td>RAAS activation</td>
<td>Neuronal degeneration/demyelination</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
<td></td>
</tr>
</tbody>
</table>

LV, left ventricular; RAAS, renin-angiotensin-aldosterone system
Empagliflozin-induced glucosuria occurs in diabetes and non-diabetes

Glucose excreted within 24 hours after single dose

- In EMPA-REG OUTCOME, the reduction in CV outcomes was consistent between 10 mg and 25 mg doses of empagliflozin.
- A difference in the magnitude of glucosuria seen between 10 mg and 25 mg doses (and diabetes vs non-diabetes) may be unlikely to impact the risk of CV outcomes with empagliflozin.

Therefore, any potential association between empagliflozin-induced glucosuria and CV risk reduction may also be seen in T2D and non-diabetes.

Transient urinary sodium excretion with empagliflozin is observed in non-diabetes and in patients with T2D.

Therefore, any potential association between empagliflozin-induced natriuresis and CV risk reduction may also be seen in non-diabetes.

*p<0.01 versus baseline; †Baseline defined as mean of four 24-hour urine collections
Rationale for exploring empagliflozin for the treatment of heart failure in patients without diabetes

Patients with HF have similar pathophysiological features as patients with diabetes\(^1,2\)

Glucosuria, natriuresis and metabolic effects of empagliflozin are seen in patients with and without diabetes\(^3-5\)

The CV benefits observed in EMPA-REG OUTCOME were largely independent of glucose levels\(^6\)

Hypothesis: Patients with HF without diabetes may benefit from empagliflozin

There is mechanistic rationale to investigate the CV outcomes of empagliflozin beyond T2D

HF, heart failure
• **Aim:** evaluate efficacy and safety of once-daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction or reduced ejection fraction

• EMPEROR HF-Preserved [NCT03057951]: n~4,100

• EMPEROR HF-Reduced [NCT03057977]: n~2,800

Patients with and without diabetes included

Follow-up: Event-driven (estimated end 2020)

**Primary endpoint:** CV death or adjudicated hospitalisation for heart failure
## Randomised controlled trials of SGLT2 inhibitors in HF beyond diabetes

<table>
<thead>
<tr>
<th></th>
<th>EMPEROR-Preserved(^1)</th>
<th>EMPEROR-Reduced(^2)</th>
<th>Dapa-HF(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>4126</td>
<td>2850*</td>
<td>4500</td>
</tr>
</tbody>
</table>
| **Key inclusion criteria** | • Patients with chronic HF\(^\dagger\)  
• Elevated NT-proBNP  
• eGFR ≥20 ml/min/1.73 m\(^2\) | • Symptomatic HFrEF\(^\dagger\)  
• Elevated NT-proBNP  
• eGFR ≥30 ml/min/1.73 m\(^2\) | |
| **Primary endpoint** | • Time to first event of adjudicated CV death or adjudicated HHF | • Time to first occurrence of CV death, HHF or urgent HF visit | |
| **Key secondary endpoints** | • Individual components of primary endpoint  
• All-cause mortality  
• All-cause hospitalisation  
• Time to first occurrence of sustained reduction of eGFR  
• Change from baseline in KCCQ | • Total number of HHF or CV death  
• All-cause mortality  
• Composite of ≥50% sustained eGFR decline ESRD or renal death  
• Change from baseline in KCCQ | |
| **Start date**   | March 2017               | March 2017            | February 2017 |
| **Expected completion date** | June 2020               | June 2020             | December 2019 |

\(^*\)NT-proBNP-based enrichment of the population with patients at higher severity of HF; \(^\dagger\)NYHA class II–IV  
eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SGLT2, sodium-glucose co-transporter-2

Heart Failure: The next frontier for SGLT2 inhibitors?

- Patients with **diabetes** exhibit a **high risk** to develop **heart failure**
- SGLT2 inhibitors reduce **HF hospitalisation** in patients with and without HF / ASCVD
- Some of the effects of **SGLT2 inhibitors** are **independent of the presence of diabetes**
- Ongoing studies will show whether **SGLT2 inhibitors** may become a **therapeutic tool** in HF patients without diabetes